Pharmaceutical Approval Update

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Fluticasone Furoate/Vilanterol Inhalation Powder (Breo Ellipta)

Manufacturer: GlaxoSmithKline, Research Triangle Park, N.C./Theravance, San Francisco, Calif.

Indication: Breo Ellipta is used for the once-daily maintenance treatment of airflow limitation in patients, 18 years of age and older, with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. It is also approved to reduce exacerbations of COPD.

Drug Class: Breo Ellipta combines an inhaled synthetic trifluorinated corticosteroid (fluticasone furoate) and a long-acting beta$_2$-adrenergic agonist (LABA) called vilanterol. The medication acts as an anti-inflammatory agent and a smooth-muscle relaxant around the airways.

Uniqueness of Product: The powder increases airflow. In *in vitro* and *in vivo* models, fluticasone furoate activated the glucocorticoid response element, blocked pro-inflammatory transcription factors (e.g., nuclear factor–kappa light chain enhancer of activated B cells B [NF-κB]), and inhibited antigen-induced lung eosinophilia in sensitized rats. Fluticasone furoate *in vitro* exhibits a binding affinity for the human glucocorticoid receptor that is approximately 29.9 times that of dexamethasone and 1.7 times that of GlaxoSmithKline's fluticasone propionate (e.g., Flonase and Flovent). In *in vitro* tests, the functional selectivity of vilanterol was similar to that of another LABA, salmeterol xinafoate (Serevent Diskus, GlaxoSmithKline).

Beta$_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle; beta$_1$-receptors are the predominant receptors in the heart. Beta$_2$-receptors in the heart make up 10% to 50% of the total number of beta-adrenergic receptors. The precise function of these receptors is not clear, but the data suggest that even highly selective beta$_2$-agonists might have cardiac effects.

The mechanism by which fluticasone furoate affects COPD symptoms is not known. Corticosteroids have various actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.

The pharmacological effects of beta$_2$-adrenoceptor agonists, including vilanterol, are in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to 3′5′-cyclic adenosine monophosphate (cAMP). Increased cAMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Boxed Warning: LABAs may increase the risk of asthma-related death. In a trial comparing salmeterol with placebo, with each added to usual asthma therapy, there were more asthma-related deaths in patients receiving salmeterol. This finding is considered a class effect of LABAs, including vilanterol. Breo Ellipta is not indicated for the treatment of asthma.

Warnings and Precautions:

Asthma-related death. Data from a large placebo-controlled trial in subjects with asthma suggested that LABAs might increase the risk of asthma-related death. It is not known whether the rate of death in patients with COPD is increased by LABAs.

A 28-week trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol. No studies have been adequately powered to determine whether the rate of asthma-related deaths is increased with Breo Ellipta. Therefore, Breo Ellipta should not be used to treat asthma.

Deteriorating disease and acute episodes. Breo Ellipta should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD, and it should not be used to relieve acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled short-acting beta$_2$-agonist. When beginning Breo Ellipta therapy, patients who have been taking oral or inhaled short-acting beta$_2$-agonists routinely (e.g., four times per day) should discontinue the regular use of these drugs and should use them only to relieve acute respiratory symptoms. When prescribing Breo Ellipta, clinicians should also prescribe an inhaled, short-acting beta$_2$-agonist and should instruct patients on how it should be used.

The condition of patients with COPD may deteriorate over a period of hours or over several days or longer. If Breo Ellipta is no longer controlling symptoms of bronchoconstriction, if an inhaled, short-acting beta$_2$-agonist becomes less effective, or if a higher dose of the short-acting beta$_2$-agonist is needed, these signs may indicate deteriorating COPD. The patient and the COPD regimen should be re-evaluated. Increasing the daily dose beyond the recommended dose is not appropriate in this situation.

Avoiding overdoses. Patients should not use Breo Ellipta more often than recommended or at higher doses than recommended. Cardiovascular effects and fatalities have been reported with the excessive use of inhaled sympathomimetic drugs. Patients using Breo Ellipta should not use another agent containing a LABA, such as salmeterol (Serevent), formoterol fumarate (Foradil, Merck/Schering) arformoterol tartrate inhalation solution (Brovana, Sunovion), or indacaterol inhalation powder (Arcapta Neohaler, Novartis) for any reason.

Effects of inhaled corticosteroids. In clinical trials, localized infections of the mouth and pharynx with *Candida albicans* have occurred with the use of fluticasone furoate/vilanterol. Candidal infections should be treated with appropriate antifungal therapy while treatment with Breo Ellipta continues; however, the inhaler therapy might sometimes need to be interrupted. Patients should be advised to rinse the mouth without swallowing after inhalation to decrease the risk of

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oropharyngeal candidiasis.

Pneumonia. In clinical trials, an increased incidence of pneumonia was observed in patients with COPD who received fluticasone furoate/vilanterol, including the 100-mcg/25-mcg dose. There was also an increased incidence of pneumonia resulting in hospitalization and, in some cases, fatalities. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD because the clinical features of pulmonary infections overlap with the symptoms of COPD exacerbations.

In replicate 12-month trials in 3,255 subjects with COPD who had experienced an exacerbation of COPD in the previous year, there was a higher incidence of pneumonia in those receiving fluticasone furoate/vilanterol 50 mcg/25 mcg (in 6%), 100 mcg/25 mcg (in 6%), or 200 mcg/25 mcg (in 7%) than in subjects receiving vilanterol 25 mcg (3%). There were no fatal cases of pneumonia in patients receiving vilanterol or fluticasone furoate/vilanterol 50 mcg/25 mcg. One patient with pneumonia who received fluticasone furoate/vilanterol 100 mcg/25 mcg died, and seven patients with pneumonia who received a dose of 200 mcg/25 mcg died (at rates below 1% in each treatment group).

Immunosuppression. Patients who take immunosuppressive drugs are more susceptible to infections than healthy individuals. In children or adults who have not had measles or who have not been properly immunized, care should be taken to avoid exposure to corticosteroids, such as fluticasone. Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Switching from systemic corticosteroids. Particular care is needed for patients being transferred from systemically active to inhaled corticosteroids. Death caused by adrenal insufficiency has occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, it takes several months for hypothalamic–pituitary–adrenal (HPA) function to be restored. Patients who have been previously maintained on 20 mg or more of prednisone may be most susceptible, particularly when systemic corticosteroids are almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, infection, or other conditions associated with severe electrolyte loss. Although Breo Ellipta may control COPD symptoms during these episodes, in recommended doses it supplies less than the normal physiological amount of glucocorticoid systemically and does not provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe COPD exacerbation, patients who have stopped using systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact a physician. They should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe COPD exacerbation.

After switching to Breo Ellipta, patients who need oral corticosteroids should be weaned slowly from systemic corticosteroids. The daily prednisone dose can be reduced by 2.5 mg each week during therapy with Breo Ellipta. Lung function, beta-agonist use, and COPD symptoms should be monitored while oral corticosteroids are being withdrawn. Patients should also be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension. Switching patients to Breo Ellipta may unmask allergic conditions previously suppressed by systemic corticosteroids, such as rhinitis, conjunctivitis, eczema, arthritis, and eosinophilia. During withdrawal from oral corticosteroids, some patients may experience joint or muscular pain and depression despite maintenance of even improved respiratory function.

Hyperadrenocorticism and adrenal suppression. Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active. Its effects on the HPA axis are not observed with the therapeutic dose of Breo Ellipta, but exceeding the recommended dosage or taking the drug with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction.

Because of the possibility of significant systemic absorption of inhaled corticosteroids in sensitive patients, patients using Breo Ellipta should be observed for systemic corticosteroid effects such as hyperadrenocorticism (Itsenko–Cushing syndrome) and adrenal suppression, including adrenal crisis. If these effects occur, the Breo Ellipta dose should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other therapies for COPD symptoms should be considered.

Drug interactions. Caution should be used when prescribing Breo Ellipta with long-term treatment with ketoconazole (Nizoral, Janssen) and with other known strong CYP3A4 inhibitors such as ritonavir (Norvir, AbbVie), clarithromycin (Biaxin, AbbVie), conivaptan (Vaprisol, Astellas), indinavir (Crixivan, Merck), itraconazole (Sporanox, PriCara/Janssen), lopinavir/ritonavir (Kaletra, AbbVie), nefazodone (Serzone, Bristol-Myers Squibb), nelfinavir (Viracept, Pfizer), saquinavir (Invirase, Genentech), telithromycin (Ketek, Sanofi), troleandomycin (not sold in the U.S.), and voriconazole (Vfend, Pfizer). Increased systemic corticosteroid and cardiovascular adverse effects may result.

Paradoxical bronchospasm. As with other inhaled agents, Breo Ellipta can produce paradoxical bronchospasm, which may be life-threatening. If it occurs, patients should use an inhaled short-acting bronchodilator. Breo Ellipta should be discontinued immediately, and an alternative therapy should be used.

Hypersensitivity. Hypersensitivity reactions may occur after the administration of Breo Ellipta. Anaphylactic reactions have been reported in patients with severe milk protein allergy after inhalation of other powder products containing lactose. Patients with severe milk protein allergy should not take Breo Ellipta.

Cardiovascular effects. Vilanterol, like other $beta_2$-agonists, can produce cardiovascular effects. Some patients may experience increases in pulse rate, systolic or diastolic blood pressure, supraventricular tachycardia, or extrasystoles. If such effects occur, Breo Ellipta may need to be discontinued.

Beta-agonists may also produce electrocardiographic changes, such as flattening of the T wave, prolongation of the corrected QT (QTc) interval, and ST-segment depression. In healthy subjects, large doses—at four times the vilanterol dose—of inhaled fluticasone furoate/vilanterol have been

associated with prolongation of the QTc interval, which has the potential to produce ventricular arrhythmias. Therefore, Breo Ellipta, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Reduced bone density. Decreases in bone mineral density (BMD) have been observed with the long-term administration of products containing inhaled corticosteroids. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care.

Because patients with COPD often have multiple risk factors for reduced BMD, an assessment of BMD is recommended before and periodically after Breo Ellipta is taken. If BMD is reduced significantly and Breo Ellipta is still considered important for the patient's COPD therapy, a medication to treat or prevent osteoporosis should be considered.

In replicate 12-month trials in 3,255 subjects with COPD, bone fractures were reported in 2% of subjects receiving fluticasone furoate/vilanterol 50 mcg/25 mcg, 100 mcg/25 mcg, or 200 mcg/25 mcg compared with fewer than 1% of those receiving vilanterol 25 mcg alone.

Ocular problems. Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD following the long-term administration of inhaled corticosteroids. Close monitoring is warranted in patients with a change in vision or with a history of these ocular conditions. In replicate 12-month trials in 3,255 subjects with COPD, similar incidences of ocular effects were reported with fluticasone furoate/vilanterol 50 mcg/25 mcg (less than 1%); 100 mcg/25 mcg (1%); 200 mcg/25 mcg (less than 1%) compared with vilanterol 25 mcg alone (1%).

Coexisting conditions. Like all drugs containing sympathomimetic amines, Breo Ellipta should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Intravenous doses of albuterol (e.g., Ventolin, GlaxoSmithKline), a related beta$_2$-adrenoceptor agonist, have had worsening effects on pre-existing diabetes mellitus and ketoacidosis.

Hypokalemia and hyperglycemia. Beta-adrenergic agonists may produce hypokalemia, possibly through intracellular shunting, which may lead to adverse cardiovascular effects. The decrease in serum potassium is usually transient. Beta-agonists may produce transient hyperglycemia in some patients. In four clinical trials lasting 6 to 12 months, there was no evidence of a treatment effect on serum glucose or potassium.

Dosage and Administration: The recommended dose of Breo Ellipta is 100 mcg/25 mcg once daily as one oral inhalation. After inhalation, patients should rinse their mouth with water without swallowing to reduce the risk of oropharyngeal candidiasis. Breo Ellipta should be taken at the same time every day and should not be used more than once every 24 hours. No dosage adjustments are needed for geriatric patients or patients with hepatic or renal impairment.

Commentary: COPD symptoms include chest tightness, cough, and excessive phlegm. Cigarette smoking is the leading cause of COPD, the third leading cause of death in the U.S.

An FDA advisory committee voted 9–4 supporting approval of the long-term maintenance and exacerbation-reduction indications for Breo Ellipta (however, not for treating sudden breathing problems). Some committee members did express concern that vilanterol—the LABA component—provided nearly all of the clinical benefit. Some panelists also had concerns about the increased risk of pneumonia (in 3%), bone fractures in clinical trials (in 2%), and the high dropout rate in the trials. In summary, the panelists concurred that once-daily use might improve medication adherence.

Sources: www.fda.gov; www.gsk.com

Atorvastatin/ Ezetimibe Tablets (Liptruzet)

Manufacturer: Merck, Whitehouse Station, N.J.

Indication: A combination of atorvastatin (Lipitor, Pfizer) and ezetimibe (Zetia, Merck/Schering) has been approved for decreasing low-density lipoprotein-cholesterol (LDL-C) levels in patients with primary or mixed hyperlipidemia as an adjunct to dietary changes. Liptruzet is also used to reduce cholesterol in patients with homozygous familial hypercholesterolemia (FH).

Drug Class: Atorvastatin calcium, a statin, is described chemically as [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1). Its molecular weight is 1155.37. The chemical name of ezetimibe, a selective cholesterol-absorption inhibitor, is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. Its molecular weight is 409.4.

Uniqueness of Drug: Atorvastatin inhibits the production of cholesterol in the liver, and ezetimibe inhibits the absorption of cholesterol in the digestive tract.

ATORVASTATIN

Warnings and Precautions:

Myopathy and rhabdomyolysis. Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and other drugs in this class. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Like other statins, atorvastatin occasionally causes myopathy in conjunction with increased levels of creatine phosphokinase (CPK) values exceeding 10 times the upper limit of normal (ULN). The concomitant use of higher doses of atorvastatin with cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy and rhabdomyolysis.

An autoimmune disease, immune-mediated necrotizing myopathy has been associated with statin use. Patients experience proximal muscle weakness and elevated serum creatinine kinase levels, which persist even after statins are discontinued. Muscle biopsy shows necrotizing myopathy without significant inflammation; improvement is achieved with immunosuppressive drugs.

Myopathy should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, or marked elevations of CPK. Patients should be advised to report unexplained muscle symptoms, particularly if they are accompanied by malaise or fever or if signs and symptoms persist after discontinuing

Liptruzet. If markedly elevated CPK levels occur or if myopathy is diagnosed or suspected, Liptruzet should be discontinued.

The risk of myopathy during treatment with statins is increased with the concurrent administration of cyclosporine, fibric acid derivatives, erythromycin (Eryc, Warner Chilcott; Ery-Tab, Abbott), clarithromycin, the hepatitis C protease inhibitor telaprevir (Incivek, Vertex), HIV protease inhibitor combinations such as saquinavir/ritonavir, lopinavir/ritonavir, tipranavir (Aptivus, Boehringer Ingelheim) plus ritonavir (Norvir), darunavir (Prezista, Janssen)/ritonavir, fosamprenavir (Lexiva, GlaxoSmithKline/Vertex) plus ritonavir, fosamprenavir alone, lipid-modifying niacin, and azole antifungals.

Patients should be monitored for signs or symptoms of muscle problems, especially during the initial months of therapy and whenever the atorvastatin dose is titrated upward. Lower starting and maintenance doses of Liptruzet should be considered when it is taken with the aforementioned drugs or combinations. Periodic CPK determinations may be considered, but there is no assurance that monitoring will prevent severe myopathy.

Liver enzymes. Statins have been linked to biochemical abnormalities of liver function. In clinical trials, persistent elevations (more than three times the ULN occurring on two or more occasions) in serum transaminases occurred in 0.7% of atorvastatin patients. The incidence of these abnormalities was 0.2% for 10 mg, 0.2% for 20 mg, 0.6% for 40 mg, and 2.3% for 80 mg.

In the trials, jaundice developed in one patient. Increases in liver enzymes in other patients were not associated with jaundice or other clinical signs or symptoms. When the atorvastatin dose was reduced and therapy was interrupted or discontinued, transaminase levels returned to pretreatment levels without sequelae. Of 30 patients with persistent transaminase elevations, 18 patients continued treatment with a reduced dose of atorvastatin.

Ezetimibe

Warnings and Precautions:

Myopathy and rhabdomyolysis. In clinical trials, no excessive myopathy or rhabdomyolysis was associated with ezetimibe compared with placebo or statins alone. The incidence of CPK exceeding more than 10 times the ULN was 0.2% for ezetimibe, 0.1% for placebo, 0.1% for ezetimibe when given with a statin, and 0.4% for statins alone. The risk of skeletal muscle toxicity is increased with higher statin doses, age over 65, hypothyroidism, renal impairment, and the concomitant use of other drugs.

Muscle problems have been reported in postmarketing experience with ezetimibe. Most patients who developed rhabdomyolysis were taking a statin before initiating ezetimibe. However, rhabdomyolysis has been reported with ezetimibe monotherapy and with the addition of ezetimibe to agents known to be associated with increased risk of rhabdomyolysis, such as fibric acid derivatives. The presence of muscle symptoms and a CPK level exceeding 10 times the ULN indicates myopathy.

Liver enzymes. In controlled clinical studies, the incidence of consecutive elevations (three or more times the ULN) in hepatic transaminase levels was similar between ezetimibe (0.5%) and placebo (0.3%). In controlled combination studies of ezetimibe plus atorvastatin, the incidence of consecutive hepatic enzyme elevations (three or more times the ULN) was 0.6% for patients receiving ezetimibe/atorvastatin. These elevations were generally asymptomatic and were not associated with cholestasis. Transaminase levels returned to baseline values after therapy was interrupted or discontinued.

Liptruzet

If Liptruzet and a fenofibrate agent are taken concomitantly, both drugs should be discontinued immediately if myopathy occurs.

Liver enzyme test results should be obtained before Liptruzet therapy starts and should be repeated as indicated. There have been rare postmarketing reports of fatal and nonfatal hepatic failure in patients taking statins, including atorvastatin. If serious liver injury with clinical symptoms or hyperbilirubinemia or jaundice occurs, Liptruzet should be promptly interrupted. If an alternative cause is not found, the drug should not be resumed.

Liptruzet should be used with caution in patients who drink substantial quantities of alcohol or who have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of Liptruzet.

Dosage and Administration: The recommended starting dose of Liptruzet is 10/10 mg/day or 10/20 mg/day. Liptruzet can be taken as a single dose at any time of the day, with or without food. The recommended starting dose for patients who require a larger reduction in LDL-C levels (greater than 55%) is 10/40 mg/day. After initiation or upon titration of Liptruzet, lipid levels should be evaluated within 2 or more weeks and the dosage should be adjusted accordingly.

The dose of Liptruzet in patients with homozygous familial hypercholesterolemia is 10/40 mg/day or 10/80 mg/day. Liptruzet should be used as an adjunct to other lipid-lowering treatments (such as LDL-C apheresis) in these patients or if such treatments are unavailable.

Liptruzet should be taken either 2 hours before or more than 4 hours after administration of a bile acid sequestrant.

If patients are taking cyclosporine, the HIV protease inhibitor tipranavir/ritonavir (Aptivus/Norvir), or the hepatitis C protease inhibitor telaprevir (Incivek), Liptruzet should be avoided.

In patients with HIV infection taking lopinavir/ritonavir (Kaletra), the lowest necessary dose of Liptruzet should be prescribed.

In patients taking clarithromycin (Biaxin) or itraconazole (Sporanox), or in patients with HIV taking fosamprenavir (Lexiva) or a combination of saquinavir/ritonavir, darunavir/ritonavir, or fosamprenavir/ritonavir, the Liptruzet dose should be limited to 10/20 mg. Appropriate clinical assessment is recommended to ensure that the lowest Liptruzet dose is used.

For patients taking nelfinavir (Viracept) for HIV infection or boceprevir (Victrelis, Merck) for hepatitis C, the Liptruzet dose should be limited to 10/40 mg. The lowest dose of Liptruzet should be prescribed. Liptruzet and gemfibrozil (Lopid, Pfizer) should not be taken together.

Commentary: The Zetia/statin approach isn't new; Merck already sells Vytorin (Zetia with its own off-patent statin, Zocor [simvastatin]). Liptruzet comes with similar questions about its real-world benefits. In announcing the approval, Merck clarified that in trials Liptruzet lowered cholesterol levels better than generic atorvastatin alone but added that the combination did not reduce the chances of developing heart disease. No incremental benefit of Liptruzet on cardiovascular morbidity

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and mortality over and above that shown for atorvastatin was established.

Sources: www.merck.com; www.dailyfinance.com, May 5, 2013; FreshNews.com; *The Wall Street Journal,* May 3, 2013

Radium 223 Dichloride Injection (Xofigo)

Manufacturer: Bayer, Wayne N.J./ Algeta US LLC, Cambridge, Mass.

Indication: Formerly known as alpharadin, radium-223 is used to treat symptomatic late-stage, castration-resistant prostate cancer in men with bone metastases and no known visceral metastatic disease after medical or surgical therapy to lower testosterone levels.

Drug Class: Radium-223 is an alpha particle–emitting radioactive pharmaceutical agent that mimics calcium and complexes with bone mineral hydroxyapatite at areas of increased bone turnover, such as bone metastases.

Uniqueness of Drug: Radiation is delivered directly to bone tumors, limiting damage to surrounding healthy tissues. Radium is taken up by the osteoblasts, and alpha radiation is emitted. This causes breaks in double-stranded DNA to eradicate cancer cells.

Warnings and Precautions:

Bone marrow suppression. Blood counts should be obtained before treatment begins and before every dose is given. Therapy should be stopped if hematological values do not recover within 6 to 8 weeks after treatment. Patients with compromised bone marrow reserve should be closely monitored. Radium-223 should be discontinued in patients who experience life-threatening complications despite supportive care measures.

Adverse drug events. The most common adverse drug reactions were nausea, diarrhea, vomiting, and peripheral edema. Hematological laboratory abnormalities included anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia.

Dosage and Administration: The IV dose is 50 kBq (1.35 microcuries) per kg, given at 4-week intervals for six injections.

Commentary: According to the American Cancer Society, prostate cancer is the leading cancer type among men after skin cancer. Prostate cancer affects about 239,000 American men each year, causing nearly 30,000 deaths.

Radium-22 was approved more than 3 months ahead of the product's goal date of August 14, 2013. This drug should be received, used, and given only by authorized persons in designated clinical settings. Administration is associated with potential risks to other persons from radiation or contamination from spills of bodily fluids; therefore, radiation protection precautions must be taken in accordance with national and local regulations.

Radium-223 is the second prostate cancer drug approved by the FDA within the previous 12 months that has the potential to extend survival. Enzalutamide (Xtandi, Astellas/Medivation) was approved in August 2012 for men with recurrent or metastatic hormone-resistant prostate cancers and who had received docetaxel (Taxotere, Sanofi).

Sources: GlobalData, WebMd, May 15, 2013; www.Xofigo-us.com; FDA, www.accessdata.fda.gov/drugsatfda_docs/label/2013/203971lbl.pdf; www.cdc.gov/cancer/skin/statistics; www.cancer.gov/cancertopics/types/melanoma ■